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(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS WITH MODIFIED RELEASE OF THE ACTIVE INGREDIENT

(57) Abstract: The present invention relates to modified-release oral pharmaceutical compositions containing one or more active principles solubilised, suspended or embedded in a suitably formulated amphiphilicmatrix which, loaded in hydrophilic matrices, provides different release profiles.

ORAL PHARMACEUTICAL COMPOSITIONS WITH MODIFIED RELEASE OF THE ACTIVE INGREDIENT

The present invention relates to modified-release oral pharmaceutical compositions containing one or more active principles solubilised, suspended or embedded in an amphiphilic matrix suitably formulated which, loaded in hydrophilic matrices, provides different release profiles. The compositions of the invention are able to modulate the *in vitro* and *in vivo* performances of those drugs which require repeated daily administrations or which have to be carried and released at specific sites of the gastrointestinal tract.

Formulation of drugs in amphiphilic matrix systems, with other surfactants, cyclodextrins and/or polymers and other excipients which are used for obtaining pharmaceutical forms having suitable technological properties, allows to increase and modulate the *in vitro* dissolution rate and to attain the prompt release of the active ingredient. Furthermore, amphiphilic systems provide homogeneous distribution of active principles having different chemical-physical characteristics (lipophilic and hydrophilic drugs) in the formulations. The amphiphilic matrix, once loaded in hydrophilic matrix systems, which swell upon contact with biological fluids, is able to modulate the homogeneous release of the active ingredient at a constant rate, to provide suitable release kinetics.

The modified-release compositions of the invention may contain active principles belonging to the therapeutical classes of analgesic, anti-inflammatory, antineoplastic, immunomodulating, antihemetic, antidiabetic, cardiovascular, hypnotic, tranquilizing, antihistamine drugs.

TECHNOLOGICAL BACKGROUND

A sustained-, delayed-, extended-, controlled- or anyway modified-

release formulation can be prepared according to different known techniques:

Use of inert matrices, in which the main structural component is a highly lipophilic material having poor affinity to biological fluids, which affords some resistance to penetration of said fluids.

Use of hydrophilic matrices, in which the structural component affords a marked resistance to wetting and solubilization in biological fluids, as the system tends to form gels and to gradually swell in time.

Use of bioerodible and/or biodegradable matrices, in which the used polymers and materials gradually undergo metabolic and/or physiological degradation at certain biological sites.

Use of mixed matrices, which comprises the use of inert lipophilic matrices with hydrophilic systems or 3-matrix- systems, i.e. hydrophilic-amphiphilic-lipophilic matrices, where different interactions with different release kinetics take place.

All the above mentioned procedures suffer, however, from some drawbacks and disadvantages.

Inert matrices generally provide non-linear but exponential release kinetics of the active ingredient.

Hydrophilic matrices have at first a straight line dissolution profile then after a certain part of the active ingredient has been released, they deviate from release linearity.

Bioerodible and/or biodegradable matrices require the ideal enzyme and/or biological environment for the constant release of the drug.

Mixed matrices consist of suitably mixed lipophilic and hydrophilic matrices combined or by lipophilic, amphiphilic and hydrophilic matrices. Although being a progress as for modified release, they do not contain materials able to improve and guarantee restricted release of the drug as

well as homogeneous absorption in the gastrointestinal tract, after the drug has been released.

When a modified-release formulation of a drug having either topical activity in the gastrointestinal tract or systemic activity is required, the controlled release has to be ensured from the very first moment after the administration. A somewhat homogeneous release range in time is also necessary, while ensuring, after an amount of the active ingredient has been released, the rapid activity of the drug both topically and systemically, thanks to it being present as microemulsion, solubilized or complexed.

DISCLOSURE OF THE INVENTION

This object has been attained according to the present invention, through the combination of a specific amphiphilic matrix, single or complex, suitably formulated and subsequently embedded in superficially hydrophilic matrix. The inventors did not take into consideration lipophilic matrices. Amphiphilic matrices were suitably selected and formulated for balancing any fast onset phase of the amount of drug present at the surface, for homogeneously modulating all the release phases from the system, including the ability for the formulation to be homogeneously absorbed, without losing the effectiveness of the system.

More particularly, the modified-release pharmaceutical compositions of the invention comprise:

1. a matrix consisting of amphiphilic compounds either liquid or with melting point below 60°C, possibly to form eutectic mixture melting at 35-37°C, in which the active ingredient is at least partially soluble and/or dispersed and/or inglobated or granulated with amphiphilic compound previously solubilised or suspended in solvent (preferably water);
2. a surface acting component which is compatible with the amphiphilic

matrix and can be homogeneously solubilized and/or dispersed in the amphiphilic matrix;

3. a component based on cyclodextrins and/or polymers which can be dispersed in the surface-activated amphiphilic matrix or can in turn be loaded on the amphiphilic matrix, either surface-activated or not, to obtain a liquid, semisolid or solid form;
4. a hydrophilic matrix in which the complex amphiphilic matrix is dispersed and part of the active ingredient can be dispersed;
5. any other excipients.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be obtained with a process which comprises the following steps:

a) adding surfactants to the amphiphilic matrix, to obtain a homogeneous solution or dispersion;
b) solubilizing, suspending, dispersing, totally or partly embedding one or more active principles;
c) adding cyclodextrins and/or polymers, or granulating or dispersing with cyclodextrins and/or polymers;
d) adding a hydrophilic matrix;
e) optionally adding excipients;
f) optionally film-coating with cellulose derivatives or methacrylic polymers.

More particularly, according to the present invention:

In **step a)** the surface-activated amphiphilic matrix is prepared. First any amphiphilic semisolid excipients or mixtures thereof are melted above 60°C, or solubilised or suspended in solvent (preferably water), to obtain a homogeneous solution and/or dispersion, which becomes again semisolid or solid at room temperature, with eutectic properties at temperatures ranging

from 35°C to 37°C (body temperature) or able to be used as granulating system. Afterwards, said excipients, which have become liquid upon melting or are already liquid at room temperature, are added with surfactants to obtain a homogeneous dispersion.

In **step b)**, the active ingredient is solubilised, dispersed and/or inglobated in the surface-activated amphiphilic matrix from step a) to obtain a homogeneous solution and/or dispersion and/or granules.

In **step c)**, the system from step (b) is added with different amounts of cyclodextrins and/or polymers until homogeneous dispersion. Alternatively, the system from step (b) can be loaded onto cyclodextrins and/or polymers and/or mixtures thereof to obtain powder, microgranules or granules having good free-flowing and/or tabletting characteristics.

In **step d)**, one or more hydrophilic excipients, which undergo marked swelling in the presence of water (hydrogels), may be added.

In **step e)**, excipients with different functions, to transform liquid or semisolid formulations into solid ones for the preparation of capsules, tablets, granulates, microgranules, minitablets, sachets may be added, such as silica, celluloses, starches, sugars, polyvinyl pyrrolydones, methacrylates, glidants, antiaggregants, lubricants such as magnesium stearate, stearic acid, talc.

Amphiphilic compounds for use in the present invention comprise glycol alkyl ethers such as diethylene glycols monoethyl ether (Transcutol), macrogolglycerids consisting of mixtures of mono-of and triglycerids and of polyethylene glycols and fatty acids (gelucire 44/14; gelucire 50/13) mono and diesters, polyethylene glycols hydroxystearates (Solutol HS 15).

Surfactants for use for use in the present invention comprise phosphatides and lecithins (phosphatidyl cholines, phosphatidyl diethanolamines, sphyngomyelins), anionic and non-ionic emulsifying

waxes, sodium lauryl sulfate, sodium dodecyl sulfate, polysorbates, cholic acids, poloxamer, sodium sulfosuccinate, sodium lauryl sarcosinate, dioctylsodium sulfosuccinate.

Cyclodextrins and polymers for use for use in the present invention comprise alpha-beta-gamma cyclodextrins, hydroxyethylcyclodextrins, methylcyclodextrins, hydroxypropylcyclodextrins, sodium croscarmellose (Acdisol), cross-linked polyvinylpyrrolidone, amberlites (IRP 88).

The hydrophilic matrix consists of excipients named hydrogels, which undergo molecular relaxation when passing from the anhydrous to the hydrate state, thus inducing remarkable increase in the system volume, hindrance and weight, due to the coordination of a large number of water molecules by the polar groups in the polymer chain. Examples of hydrogels for use in the invention, comprise substances selected from acrylic or methacrylic polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, alginates, pectins, starches and derivatives, natural and synthetic gums, polycarbophil, chitosans.

According to a general procedure of the invention, an amphiphilic matrix is first is prepared in the form of a mixture soluble or melted at temperatures above 60°C and/or solubilised and/or dispersed in solvents (preferably water), containing one or more amphiphilic materials, which is added with one or more surfactants. The amount of surfactant usually does not exceed 10% w/w, the optimum amount ranging from 0.1% to 5%.

This mixture may be added with an amount of cyclodextrin or polymer of up to 10%, the optimum amount ranging from 0.1% to 2.5%, to obtain a homogeneous dispersion.

The active ingredient may be dissolved and/or dispersed and/or granulated in this system up to concentrations ranging from 0.1% to 50%,

preferably from 0.1% to 4.9%.

Alternatively, the liquid or semisolid amphiphilic matrix may be used as granulating component. Once melted, or solubilised and /or dispersed in solvents (preferably water), this matrix containing part of the surfactants, dextrins, polymers and active ingredient solubilised or dispersed or granulated, can be added to a significant amount of polymers and/or cyclodextrins already containing the remainder of the active ingredient, to obtain a solid composition ready for further formulation with the addition of the hydrophilic matrix or with mixtures of hydrophilic matrices having different viscosity values, in weight ratios typically ranging from 99.5:0.5 to 0.5:99.5 (amphiphilic matrix : hydrophilic matrix), and of suitable adjuvants such as silica, microcrystalline celluloses, starches, lubricants. The cooled semisolid amphiphilic matrix cools, as well as the extrusion and/or granulation, promotes the compacting of the formulation, to obtain a granule or microgranule easy to process. The final pharmaceutical form may be prepared by dry- or wet- granulation with granulating excipients.

The capsules, microgranules and/or tablets can be subjected to conventional coating processes with gastro-soluble films or gastro-protected with cellulose and methacrylic polymers.

The active principles which can be conveniently formulated according to the invention comprise:

1. Antineoplastics and immunomodulators, such as: cyclophosphamide, chlorambucil, melfalan, busulfan, methotrexate, fludarabine, mercaptopurine, thioguanine, fluorouracil, tegafur, etoposide, idarubicin, procarbazine, estramustine, hydroxycarbamide, irinotecan, topotecan, tretinoin, medroxyprogesterone, megestrol, tamoxifen, toremifen, bicalutamide, flutamide, aminoglutetimide, anastrozole, exemestane, letrozole, levamisole, cyclosporin, micofenolate mofetil,

tacrolimus, doxorubicin, epirubicin, dacarbazine, paclitaxel, daunorubicin.

2. Detoxicant compounds for cytostatic treatments, such as: calcium folinate, calcium levofolinate, folic acid.
3. Anti-inflammatories, analgesics and antirheumatics, such as: acetaminophen, phenacetin, sodium salicylate, acetametacin, diclofenac, fentiazac, indomethacin, proglumetacin, sulindac, cinnoxicam, meloxicam, piroxicam, tenoxicam, thiaprophenic acid, flurbiprofene, furprofene, ibuprofen, ketoprofen, naproxen, oxaprozin, mefenamic acid, niflunic acid, amtolmetin guacil, nabumetone, nimesulide, etodolac, glucosamine and its salts.
4. Drugs for the treatment of the bone diseases, such as: alendronic acid, clodronic acid, etidronic acid, risedronate.
5. Antitussives, such as: dextromethorphan, codeine phosphate, levodropropizine.
6. Systemic antihistamines, such as: mequitazine, prometazine, cetrizine, oxatomide, acrivastatin, fexofenadine, ketotifene, loratadine, mizolastine, terfenadine.
7. Antiemetics, antinausea, such as: dolasetron, granisetron, ondansetron, tropisetron, proclorperazine.
8. Antipropulsives, such as: loperamide.
9. Oral hypoglycemizining antidiabetics, such as: metformin, chlorpropamide, glybenclamide, glyclazide, glymepiride, glypizide, glyquidone, glysolamide.
10. Cathartics, such as: bisacodil, sodium picosulfate.
11. Antihypertensives, ace-inhibitor, betablocker, antiarhitmic and coronarodilators, such as: captopril, labetalol, atenolol, propafenone isosorbide mono- dinitrate, carvedilol.

12. Calcium antagonists, such as: nifedipine, nicardipine, diltiazem, verapamil.
13. Antiparkinson drugs, such as: pergolide, carbidopa, levodopa.
14. Intestinal anti-inflammatories, such as: olsalazine, 5-aminosalicylic, sulfasalazine, budesonide, ciclesonide, betamethasone, beclomethasone.
15. Anxiolytics as: chlordiazepoxide, oxazepam, medazolam, alprazolam, donazepam, lorazepam.
16. Antiepileptics, such as: valproate, carbamazepine, phenytoin, gabapentin, tiagabine, lamotrigine, topiramate, biperidene, bornaprine, metixene, procyclidine, trihexyphenidyl.
17. Alpha-Blockers, such as: doxazosin, terazosin, urapidil.
18. Diuretics, such as: chlorthalidone, fenquizone, indapamide, metolazone, xipamide, bumetanide, furosemide, piretanide, toresamide, etozolin.
19. Hypolipemizing agents such as: atorvastatin, cerivastatin, fluvastatin, pravastatin, simvastatin, lovastatin.
20. 5HT1 selective antagonists such as: rizatrepan, sumatripan, zolmitripan, pizotifen.
21. Anticholinergic such as: cimetropium bromide, otilonium bromide, prifinium bromide, scopolamine buthylbromide.
22. Lissive: mebeverine, rociverine, trimebutin.
23. Antidepressant such as: paroxetine, fluvoxamine, fluoxetine, sertraline, mirtazapine.
24. Antibiotics such as: cefadroxil, ofloxacin, ciprofloxacin, doxycyclin, erytromycin, cefaclor, ampicillin, cephradine, doxacillin, cefuroxime axetil, amoxicillin, potassium clavulanate, clarithromicin, norfloxacin.
25. Ematological such as: bromeline.

As far as dissolution characteristics are concerned, these formulations, when contacted with water or aqueous fluids, undergo modified, delayed release of the active ingredient which is present in the resulting dispersion, solubilization and/or emulsion of the system. Surfactants, cyclodextrins and polymers present in the amphiphilic structure favor wettability of the system and the homogeneous release in solution of the active principles within restricted ranges, thus promoting the continuous, gradual absorption or the gradual topical release in the gastrointestinal tract.

The following examples illustrate the invention in greater detail.

Example 1

50 g of flutamide are suspended in an kneaded with 45 g of gelucire 44/14 and 5 g of solutol HS 15 suitably melted and kept at a temperature ranging between 55°C and 65°C.

750 g of flutamide are loaded into a granulator/homogenizer and the hot mixture prepared above is added thereto. The mixture is further granulated with an aqueous solution/suspension containing 5 g of sodium lauryl sulfate and 10 g of betacyclodextrins to obtain a homogeneous granulate. 5 g of crospovidone and 80 g of hydroxypropyl methylcellulose (hydrophilic matrix) are added in succession into the granulator.

The components are mixed to homogeneous dispersion of the matrices, then 100 g of microcrystalline cellulose, 5 g of magnesium stearate, 5 g of talc and 10 g of colloidal silica are added in succession.

The final mixture is tabletted to unitary weight of 1070 mg/tablet, so that 750 mg of active ingredient per single tablet are administered.

The resulting tablets are then film coated with ethylcellulose and plasticizers.

The tablets were subjected to dissolution test in simulated gastric juices and/or intestinal environment, showing the following release profile:

after 60 minutes no more than 30%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

Example 2

45 g of gelucire 44/14 are melted and kept at a temperature ranging between 55°C and 65°C. 5 g of Transcutol are added to gelucire 44/14 under strong stirring for at least 5 minutes. The stirred mixture is added with 5 g of dioctyl sodium sulfosuccinate and 10 g of betacyclodextrins.

75 g of calcium folinate are loaded into a granulator/homogenizer and the hot mixture obtained above is added thereto. The mixture is granulated to homogeneity, then 100 g of hydroxypropyl methylcellulose (hydrophilic matrix) and 50 mg of policarbophil are added in the granulator. The components are mixed to homogeneous dispersion of the matrices, then 210 g of prosolv, 5 g of magnesium stearate and 5 g of colloidal silica are added in succession.

The final mixture is tabletted to unitary weight of 510 mg/tablet, so that 75 mg of active ingredient per single tablet are administered.

The resulting tablets are then film coated with ethylcellulose and plasticizers.

the tablets were subjected to dissolution test in gastric juices and/or in simulated intestinal environment showing the following release profile: after 60 minutes no more than 25%, after 180 minutes no more than 50%, after 5 hours no more than 70%.

Example 3

25 g of 5-FU (Fluorouracil) are suspended and impastati with 15 g of Transcutol and 5 g lecithins. 225 g of 5-FU (5-fluorouracil) are loaded into a granulator/homogenizer, and the mixture prepared above is added thereto. The mixture is further granulated with an aqueous solution containing 50 g polyvinylpyrrolidone to obtain a homogeneous granulate. 150 g of

hydroxypropyl methylcellulose (hydrophilic matrix) are added into the granulator. The components are mixed to homogeneous dispersion of the matrices and then 130 g of microcrystalline cellulose, 5 g of magnesium stearate, 5 g of talc are added in succession.

The final mixture is tabletted to unitary weight of 610 mg/tablet so that 250 mg of active ingredient per single tablet are administered.

The resulting tablets are then film coated with cellulose acetophthalate or polymethacrylates and plasticizers to ensure gastric resistance and to prevent gastric release of active ingredient.

The tablets were subjected to dissolution test in gastric juices and/or in simulated intestinal environment showing the following release profile: after 120 minutes in gastric juices 0%, after 60 minutes in enteric juice no more than 25%, after 180 minutes no more than 50%, after 6 hours no more than 80%.

Example 4

900 g of gabapentin are loaded into a granulator/homogenizer, and a molten mixture containing a suspension of 50 g of gelucire 50/14, 5 g of Solutol HS 15 and 5 g of Acdisol is added thereto. The mixture is further granulated with an aqueous solution / suspension containing 5 g of sodium lauryl sulfate and 25 g of betacyclodextrins to obtain a homogeneous granulate. 110 g of hydroxypropyl methylcellulose (hydrophilic matrix) are added in the granulator. The components are mixed to homogeneous dispersion of the matrices, then 90 g of Prosolv, 5 g of magnesium stearate, 5 g of talc and 10 g of colloidal silica are added in succession.

The final mixture is tabletted to unitary weight of 1210 mg/tablet so that 900 mg of active ingredient per single tablet are administered.

The resulting tablets are then film coated with ethylcellulose and plasticizers.

The tablets were subjected to dissolution test in gastric juices and/or in simulated intestinal environment showing the following release profile: after 60 minutes no more than 30%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

Example 5

850 g of metformin are loaded into a granulator/homogenizer and a molten mixture containing a suspension with 50 g of gelucire 44/14, 5 g of Sodium lauryl sulfate and 5 g of Acdisol is added thereto. The mixture is further granulated with an aqueous solution containing 50 g of polyvinylpyrrolidone to obtain a homogeneous granulate. 100 g of hydroxypropyl methylcellulose (hydrophilic matrix), and 50 g of policarbophyl are added in succession in the same granulator. The components are mixed to homogeneous dispersion of the matrices, then 90 g of Prosolv, 5 g of magnesium stearate, 5 g of colloidal silica are added in succession.

The final mixture is tabletted to unitary weight of 1200 mg/tablet so that 850 mg of active ingredient per single tablet are administered.

The resulting tablets are then film coated with ethylcellulose and plasticizers.

The tablets were subjected to dissolution test in gastric juices and/or in simulated intestinal environment showing the following release profile: after 60 minutes no more than 25%, after 180 minutes no more than 55%, after 6 hours no more than 80%.

As far as Metformin, the following pictures in graphics 1and 2 showed the pharmacokinetic results after the administration in 6 healthy volunteers of modified release tablet vs originator plain form. As well as indicated in the raw data available, there are significant differences into the MRT and T max data.

Example 6

15 g of gelucire 44/14 are melted and kept at a temperature ranging from 55°C and 65°C. 1.5 g of Solutol HS 15 are added thereto under strong stirring for at least 5 minutes. The stirred mixture is added with 1.5 g of dioctyl sodium sulfosuccinate and 1 g of betacyclodextrins.

10 g of Glipizide are loaded into a granulator/homogenizer and the hot mixture obtained above is added thereto. The mixture is granulated to obtain a homogeneous mixture. 50 g of hydroxypropyl methylcellulose, 10 g of policarbophyl and 17 g of betacyclodextrins granulator are added into the granulator. The components are mixed to homogeneous dispersion of the matrices, then 90 g of microcrystalline cellulose, 50 g of Prosolv, 5 g of magnesium stearate 5 g of talc and 10 g of colloidal silica are added in succession.

The final mixture is tabletted to unitary weight of 270 mg/tablet so that 15 mg of active ingredient per single tablet are administered.

The resulting tablets are then film coated with ethylcellulose and plasticizers.

The tablets were subjected to dissolution test in gastric juices and/or in simulated intestinal environment showing the following release profile: after 60 minutes no more than 25%, after 180 minutes no more than 50%, after 5 hours no more than 70%, after 6 hours no more than 80%.

Example 7

50 g of gelucire 50/13 and 10g of solutol HS 15 are suitably melted and kept at a temperature of about 60°C.

500 g of mesalamine are loaded into a granulator/ homogenizer and the hot mixture prepared above is added thereto. The mixture is further granulated with an aqueous solution/ suspension containing 5 g of sodium lauryl sulfate and 10 g of hydroxypropylmethylcellulose low viscosity to

obtain an homogeneous granulate.

150 g of hydroxypropylmethylcellulose high viscosity are added into the granulator. The components are mixed to the homogeneous dispersion of the matrix; than 100 g of microcrystalline cellulose, 5 g of magnesium stearate, 5 g of colloidal silica are added.

The final mixture is tabletted to unitary weight of 835 mg per tablet, so that 500 mg of active are administered.

The resulting tablets are film coatedwith 60 mg of polymetacrilates mixture (2L/1S) to ensure gastric resistence until pH 6,4.

The tablets were subjected to dissolution test at diffenrent pH showing the following release profile:

After 120 minutes at pH 1.2, 0%; after 60 minutes at pH 6.4 less than 5%; at pH 7.2 after 2 hours no more than 25%; after 4 hours no more than 50%, after 6 hours no more than 80%.

CLAIMS

1. Oral controlled-release pharmaceutical compositions, comprising:
   a) a matrix consisting of amphiphilic compounds either liquid or with melting point below 60°C, possibly to form eutectic mixture melting at 35-37°C, in which the active ingredient is at least partially soluble and/or dispersed and/or inglobated or granulated with amphiphilic compound previously solubilised or suspended in solvent (preferably water);
   b) a surface acting component which is compatible with the amphiphilic matrix and can be homogeneously solubilized and/or dispersed in the amphiphilic matrix;
   c) a component based on cyclodextrins and/or polymers which can be dispersed in the surface-activated amphiphilic matrix or can in turn be loaded on the optionally surface-activated amphiphilic matrix, to obtain a liquid, semisolid or solid form;
   d) a hydrophilic matrix in which the complex amphiphilic matrix is dispersed and part of the active ingredient can be dispersed;
   e) any other excipients.

2. Compositions as claimed in claim 1 wherein the amphiphilic compounds comprise glycol alkyl ethers such as diethylene glycols monoethyl ether; macrogolglycerids such as mixtures of mono-of and triglycerids and of mono- and diesters of polyethylene glycols and of fatty acids, polyethylene glycols hydroxystearates.

3. Composition as claimed in claims 1 and/or 2, wherein surfactants comprise phosphatides, phosphatidyl cholines, phosphatidyl diethanolamines, sphyngomyelins, anionic and non-ionic emulsifying waxes, sodium lauryl sulfate, sodium dodecyl sulfate, polysorbates, cholic

acids, poloxamer, sodium sulfosuccinate, sodium lauryl sarcosinate, dioctylsodium sulfosuccinate.

4. Composition as claimed in the above claims wherein cyclodextrins comprise alpha-beta-gamma cyclodextrins, hydroxyethylcyclodextrins, methylcyclodextrins, hydroxypropylcyclodextrins.

5. Composition as claimed in the above claims, wherein polymers comprise sodium croscaramellose, cross-linked polyvinylpyrrolidone, amberlites.

6. Composition as claimed in the above claims, wherein the active ingredient is in part present in the amphiphilic matrix and in part loaded on the cyclodextrins and/or polymers, in the form of minitablets, granules or microgranules.

7. Composition as claimed in the above claims, wherein the amphiphilic matrix is loaded on a hydrophilic matrix consisting of hydrogels.

8. Composition as claimed in the above claims, wherein hydrogels comprise substances selected from acrylic or methacrylic polymers or copolymers, alkylvinyl polymers, celluloses, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, alginates, pectins, starches and derivatives, natural and synthetic gums, polycarbophil, chitosans.

9. Composition according to any one of the above claims comprising a gastro-soluble or gastro-resistant coating of cellulose derivatives and/or methacrylic acid polymers.

10. Composition according to any one of the above claims, wherein the active ingredient belongs to therapeutical categories selected from antineoplastics and immunomodulators, detoxicant compounds for cytostatic treatments, anti-inflammatories, analgesics and antirheumatics, drugs for the treatment of bone diseases, antitussives, systemic antihistamines, antiemetics, antinausea agents, antipropulsives, oral hypoglycemizing

antidiabetics, cathartics, antihypertensives, ace-inhibitors, betablockers and coronarodilators, calcium antagonists, antiparkinson drugs, intestinal anti-inflammatories, anxiolytics, antiepileptics, alpha-blockers, diuretics, hypolipemizing agents, 5HT1 selective antagonists, anticholinergics, lissives, antidepressants, antibiotics.

11. Compositions as claimed in claim 7, wherein the active ingredient is selected from etoposide, calcium folinate, methotrexate, cyclophosphamide, procarbazine, fluorouracil, idarubicin, glypizide, glybenclamide, flutamide, nimesulide, piroxicam, ketoprofen, ibuprofen, gabapentin, 5-aminosalicylic, budesonide, metformin, mesalamine.

12. A process for the preparation of the compositions of claims 1 to 9, which comprises the following steps:

a) adding surfactants to the amphiphilic matrix, to obtain a homogeneous solution or dispersion;

b) solubilizing, suspending, dispersing, totally or partly embedding one or more active principles;

c) adding cyclodextrins and/or polymers, or granulating or dispersing with cyclodextrins and/or polymers;

d) adding a hydrophilic matrix;

e) optionally adding excipients;

f) optionally film-coating with cellulose derivatives or methacrylic polymers.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/06749

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/24 A61K47/40 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 76478 A (CIP-NINETY TWO-92 S.A.) 21 December 2000 (2000-12-21) claims examples page 5, line 26 -page 8, line 6	1-12
A	EP 0 514 008 A (TAKEDA CHEM. IND. LTD,JP) 19 November 1992 (1992-11-19) claims examples page 4, line 49 -page 5, line 6	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2002	05/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/06749

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0076478 A	21-12-2000	IT MI991317 A1	14-12-2000
		IT MI20000422 A1	03-09-2001
		AU 5680100 A	02-01-2001
		CN 1355693 T	26-06-2002
		WO 0076478 A1	21-12-2000
		EP 1183014 A1	06-03-2002
		NO 20016108 A	24-01-2002
		TR 200200562 T2	21-05-2002
EP 514008 A	19-11-1992	AT 149348 T	15-03-1997
		CA 2066384 A1	20-10-1992
		DE 69217711 D1	10-04-1997
		DE 69217711 T2	17-07-1997
		DK 514008 T3	12-05-1997
		EP 0514008 A1	19-11-1992
		ES 2098447 T3	01-05-1997
		GR 3023383 T3	29-08-1997
		JP 3272029 B2	08-04-2002
		JP 5132416 A	28-05-1993
		JP 2001354593 A	25-12-2001
		JP 2001354550 A	25-12-2001
		KR 217165 B1	01-09-1999
		SG 50480 A1	20-07-1998
		US 2002142041 A1	03-10-2002
		US 5576025 A	19-11-1996
		US 5731006 A	24-03-1998
		US 6368635 B1	09-04-2002